Human T-cell Leukemia Virus Myelopathy

HUMAN T-CELL LEUKEMIA VIRUS (HTLV-1), the first human retrovirus discovered, was found in association with adult T-cell leukemia or lymphoma in 1980. Since then, this virus has been recognized as the probable cause of some cases of tropical spastic paraplegia and the closely related, if not identical, HTLV-1–associated myelopathy in southern Japan. Both of these conditions are characterized by slowly progressive paraparesis in adults, with variable sensory manifestations, usually without remission. Because these disorders are endemic to parts of the Caribbean and to southern Japan, most of the described cases have occurred in black or Japanese patients.

The virus is transmittable by breast-feeding; the substitution of bottle feeding prevents vertical transmission. The virus is also possibly transmitted by sexual contact, shared needles, and blood transfusion. In a methadone maintenance clinic in New Orleans, Louisiana, 49% of patients were HTLV-1–positive; 5% to 14% of patients attending a sexually transmitted diseases clinic in Jamaica were HTLV-1–positive; the percentage increased with age. Cases of myelopathy due to transfusion-transmitted virus have been reported.

Recent epidemiologic studies indicate that HTLV-1 is also present in temperate climates. In the United States, the highest frequency of HTLV-1 antibody–positive persons is found in the Southeast among intravenous drug users and prostitutes. The virus is also present in the blood supply: the risk of receiving HTLV-1 by transfusion was 0.024% per unit in one US study.

Most people infected with HTLV-1 are asymptomatic. There may be a latent period of years between infection and the occurrence of clinical symptoms. The natural history of the infection and the factors influencing disease production and expression are poorly understood. Host immune responses may help determine the occurrence of inflammatory myelopathy in some infected persons but not others.

When the diagnosis of HTLV-1 myelopathy is suspected, serum and cerebrospinal fluid (CSF) specimens should be sent for HTLV-1 antibody determinations. The screening tests are done on all donor blood specimens and thus should be available in most communities. The screening test is an enzyme-linked immunosorbent assay. The test is sensitive and false-positives occur, so positive tests should be confirmed by a Western blot assay in which antibodies to various specific antigens of the HTLV-1 virus are determined.

Some findings in patients with tropical spastic paresis or HTLV-1–associated myelopathy are similar to those in multiple sclerosis: scattered white matter lesions with increased T2 signal on head magnetic resonance imaging, delayed evoked responses, and a mild pleocytosis on CSF examination, with an increase in immunoglobulin (Ig) G levels in the CSF and oligoclonal bands. Important differences are the epidemiologic pattern, the paucity of remissions, the pathologic picture, and positive HTLV-1 antibody tests in serum and CSF in patients with tropical spastic paraparesis or HTLV-1–associated myelopathy. The disorder is generally more inflammatory than seen in the usual case of multiple sclerosis; the typical plaque of multiple sclerosis has not been seen. In tropical spastic paraparesis, the virus is found in the cells in the CSF, and the increased CSF IgG is largely directed against HTLV-1.

A few early reports suggested that HTLV-1 antibody and antigen could be detected in serum and CSF in some patients with multiple sclerosis, but a large number of subsequent studies have had negative results. There is a consensus that HTLV-1 is not the cause of multiple sclerosis, but some speculate that a related and as-yet-unidentified retrovirus could be responsible.

Another syndrome associated with HTLV-1 infection is sporadic familial spastic paraplegia, a possible result of the vertical transmission of the virus through breast-feeding. Infection with HTLV-1 can also cause a fatal subacute meningoencephalitis. Reports of associations with other neurologic syndromes must be viewed cautiously, especially from endemic areas. The presence of pleocytosis and a local synthesis of IgG directed against HTLV-1, however, are presumptive evidence of a causal connection.

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Acquired Immunodeficiency Syndrome Dementia

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) dementia complex, also called AIDS encephalopathy, is the most frequent neurologic complication of AIDS. It affects 40% to 60% of patients, most commonly those with advanced immunosuppression.

The complex is characterized by a slowing of cognitive and motor abilities. Early in the course, patients show difficulties with concentration and memory, as well as apathy and social withdrawal that may be mistaken for depression. Hyperreflexia, a slowing of the rapid movements of eyes and limbs, and pathologic reflexes are commonly found on neurologic examination. Psychiatric symptoms may be prominent, and psychosis or mania may be the presenting manifestation. As the disease progresses, intellectual function continues to decline, and, although alert, patients eventually become mute, paraparetic, and incontinent. Treatment with zidovudine may result in improvement.

Cranial computed tomographic (CT) scans show increased ventricular and sulcal size, consistent with cerebral atrophy. Although CT sometimes shows white matter changes, magnetic resonance images of brain frequently show diffuse or patchy increased signals in the white matter, especially on T2-weighted images. Cerebrospinal fluid (CSF) findings in AIDS dementia complex are similar to those seen in persons infected with the human immunodeficiency virus type 1 (HIV-1) without dementia and include elevated protein levels, oligoclonal bands, intrathecal synthesis of anti–HIV-1 antibodies, and virus isolation by culture. Cerebrospinal fluid levels of HIV-1 core antigen (p24), β_2-microglobulin, and neopterin seem to correlate with the severity of dementia. The main practical value of neuroimaging and CSF examination is in excluding other opportunistic disorders that may mimic AIDS dementia complex or exist concomitantly. Neuropsychological test results show impairment in motor speed and fine control, concentration,

problem solving, and visuospatial performance. The complex remains a clinical diagnosis; neuroimaging studies, CSF examination, and neuropsychological test results support but do not establish the diagnosis.

The mechanism by which HIV-1 infection causes dementia is unclear because in brain most virus is found in macrophages and microglia, not in neurons. The HIV-1 envelope protein, gp120, can kill rodent neurons in vitro, perhaps by interfering with the neurotropic effects of vasoactive intestinal peptide, by increasing intracellular calcium concentrations, or by both mechanisms. Also, HIV-1–infected mononuclear cells release neurotoxins that kill chick and rat neurons in culture by binding to *N*-methyl-D-aspartate receptors. These data raise the possibility of specific treatments for AIDS dementia complex, such as calcium channel blockers or *N*-methyl-D-aspartate receptor antagonists.

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Treatment of Cluster Headaches

CLUSTER HEADACHE is an excruciating unilateral headache often mistaken for migraine. Recent evidence suggests different biochemical and physiologic mechanisms for each headache type. Failure to make this distinction can result in ineffectual treatment and frustration for clinicians and patients.

Cluster headache has a male to female ratio of approximately 6:1. The age of first occurrence ranges from 20 to 50 years, with a peak of between 21 and 30 years. Attacks are paroxysmal, unilateral, stabbing or piercing—rather than throbbing, as with migraines—and are usually associated with nasal stuffiness, tearing, and conjunctival hyperemia. There is no aura or throbbing sensation as with migraine. Attacks last about 45 minutes and may occur several times during the day, frequently occurring at the same time each day, often between 9 PM and 10 AM, and most often during rapid-eye-movement (REM) sleep. Headaches occur in cycles lasting from four to eight weeks, followed by a headache-free interval of several weeks to months. Subclassifications include episodic, chronic, subchronic, and a variant called chronic paroxysmal hemicrania.

Physiologic abnormalities may include a disturbance in lower brain-stem mechanisms as reflected in prolonged brain-stem auditory evoked potentials with particular prolongation of latencies I to III. Unilateral disturbances in central autonomic vasomotor function have also been found. Disturbances in histamine and serotonin sensitivity have been described, as have disturbances in REM sleep patterns, though the exact pathogenic pathways have not been established. A "trigeminovascular" pathway giving rise to cerebral hypofusion has been proposed.

Treatment is divided into symptomatic and prophylactic therapies, with variations according to headache subtype and patient compliance. For episodic cluster headaches, inhaled agents are most effective because of their rapid absorption. Ergotamine aerosol, taken one to three inhalations at the start of a headache, has been effective as much as 80% of the time provided the inhaler is shaken vigorously before use and the patient inhales each dose after a forced exhalation. Inhaling 100% oxygen through a tight mask at 7 to 10 liters per minute for 15 minutes has also been highly effective; it can be used as much as five times per day. Administering 1 ml of a 4% topical lidocaine solution intranasally ipsilateral to the headache has been effective, but it may be difficult for patients to self-administer in the throes of an acute attack. Dihydroergotamine mesylate, 1 to 2 mg given intravenously, has been reported effective if administered within the first few minutes of an attack; the parenteral or subcutaneous routes have been less successful.

The most effective prophylaxis for episodic cluster is the use of ergotamine preparations, as ergotamine tartrate, 1 to 2 mg two to three times a day taken orally, or, for nocturnal headache, 2 mg at bedtime. Methysergide maleate in a dose of 2 mg given three to four times a day, often combined with cyproheptadine, 8 mg taken at bedtime, is also useful. Calcium channel blockers, particularly verapamil, have been highly effective in episodic cluster prophylaxis, provided the cardiac and side effects of the drug can be tolerated. Alternative regimens include verapamil, 80 mg three to four times a day or 180 to 240 mg in the sustained-release form given daily; nimodipine, as much as 240 mg per day; or nifedipine, with doses ranging between 40 and 120 mg per day. Steroids given for one to two weeks can be effective used either alone or in conjunction with ergotamine preparations. The use of dexamethasone, 4 mg twice a day for two weeks, then four times a day for a week, has been recommended; it is thought to work by inhibiting histamine decarboxylases, mast cell degranulation, and histamine release. Prednisone given in large initial doses tapered over one to two weeks with subsequent alternate-day therapy has been reported as useful, though dosage schedules vary widely, with the initial doses being between 40 and 80 mg.

For patients whose headaches are refractory to the above therapies, lithium taken in daily doses ranging from 300 to 1,500 mg—with the usual range being 600 to 900 mg—titrated to the therapeutic range has been reported effective in as much as 80% of patients, although the panoply of side effects often defeats patient acceptance. A lithium citrate solution dissolved in fruit juice may reduce gastrointestinal symptoms.

Patients with constant, or chronic, cluster headaches are more difficult to treat and have been reported to have elevated scores on the Minnesota Multiphasic Personality Inventory for depression, hysteria, and addiction tendencies. Combined regimens of calcium channel blockers and ergotamine with the addition of lithium in the schedules mentioned have been advocated with varying degrees of success.

A subclass or variant, chronic paroxysmal hemicrania, has been described as similar to cluster headache but with increased frequency, shorter duration, less restlessness, and, at times, provocation of the attack by neck flexion. Unlike cluster headache, chronic paroxysmal hemicrania is said to be totally responsive to the use of indomethacin given in divided doses from 70 to 100 mg per day when tolerated.

Patients should be warned that any alcohol or tobacco use may incite attacks, though typically they will have discovered this before consulting a physician. The use of narcotic analgesics is discouraged in all but the most intractable cases and only then when given under careful supervision in a